

Application No. 10/783,054

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**Amendments to the drawings:**

Please amend the drawings by replacing Figures 1-3 (all figures) with the Replacement Sheets attached hereto in accordance with 37 C.F.R. § 1.121(d).

Attachment: Replacements Sheets (4)

### Remarks

This is in response to the Office Action of January 9, 2008. The issues raised therein are addressed below in the order originally set forth.

### **DRAWINGS.**

New corrected *Drawings* are submitted concurrently herewith, in accordance with the request of the Examiner.

### **SPECIFICATION.**

The *Brief Description of the Drawings* section has been amended to more clearly indicate the various Figures A, B, C, etc. Entry thereof and withdrawal of this rejection is respectfully requested.

### **CLAIM REJECTIONS—35 USC 103**

Claims 1, 2, 4, 5, 7-14, 16-19, 21, 28-37, 39-46, and 48-50 stand rejected as obvious under 35 USC 103(a) as being unpatentable over *Kane et al.* in view of *Hawker et al.* Reconsideration in view of the remarks set forth below is respectfully requested.

It is said in the Official Action that Kane discloses the brush polymers and suggest their use in prostheses, implanted devices, drug delivery devices, contact lenses, etc., at page 2388, first column, first paragraph. Applicant respectfully disagrees.

First, Hawker does not disclose brush polymers at all. The first paragraph of Kane et al. is inserted below:

**Surfaces that Resist Protein Adsorption.** Surfaces that resist the nonspecific adsorption of proteins<sup>2,3</sup> have (inter alia) applications in prostheses, sensors, substrates for enzyme-linked immunosorbent assays (ELISAs),<sup>4</sup> materials for use in contact lenses and implanted devices,<sup>4</sup> devices for drug delivery,<sup>5</sup> and materials for patterned cell culture.<sup>6</sup> While a number of different protein-resistant surfaces have been identified,<sup>2,3,7-12</sup> an understanding of the mechanism of their action at the molecular level is still incomplete.<sup>2,3,13-22</sup> The observation that surfaces

presenting the neutral polyether poly(ethylene glycol) (PEG) resist the nonspecific adsorption of proteins has led to the extensive use of derivatives of PEG for biomedical applications.<sup>23</sup> PEG does have the drawback that it is susceptible to autoxidation in the presence of O<sub>2</sub> and transition metal ions.<sup>24-26</sup> Furthermore, in vivo, the terminal hydroxyl group of PEG can be oxidized by alcohol dehydrogenase to an aldehyde group; the aldehyde group may react with proteins or be further oxidized by alcohol dehydrogenase.<sup>27,28</sup> These factors have led to an interest in identifying additional protein-resistant surfaces.<sup>2,3,8,11,29-31</sup>

This paragraph generally describes the need for surfaces that resist protein adsorption, but only mentions poly(ethylene glycol) and neither discloses nor suggests brush polymers

The second full paragraph of Kane et al. set forth below, goes on to describe self-assembled monolayers, but again says nothing of attaching brush polymers to those self-assembled monolayers:

*SAMs that Resist the Adsorption of Proteins.* SAMs of alkanethiolates on gold have been useful in correlating the molecular-scale structure of surfaces with their ability to resist the adsorption of proteins. SAMs presenting oligo-(ethylene glycol)  $-(\text{EG})_n\text{OH}$  and  $-(\text{EG})_n\text{OCH}_3$ ,  $n = 3-6$  groups resist the adsorption of proteins well and are the standard against which new protein-resistant surfaces are judged.<sup>3,9</sup> These SAMs are, however, not unique in their ability to resist the adsorption of proteins; SAMs presenting other functional groups (a-1, Table 1)<sup>2,3,7-9,11</sup> are also protein-resistant.<sup>32</sup>

The third full paragraph of Kane et al. goes on to discuss other protein resistant surfaces, but again says nothing of brush polymers. This paragraph is inserted below:

*Other Protein-Resistant Surfaces.* Chapman et al.<sup>30</sup> prepared polymeric films by the reaction of polyamines

(such as poly(ethyleneimine)) with SAMs presenting interchain carboxylic anhydride groups. The subsequent functionalization of the free amino groups with acetyl chloride, or with acyl chlorides that were derivatives of oligo(ethylene glycol), resulted in films that resisted the adsorption of proteins. Some surfaces derivatized with carbohydrates also resist the adsorption of proteins.<sup>9,12,33</sup> Osterberg et al.<sup>12</sup> reported that derivatives of cellulose grafted to polystyrene were nearly as effective as PEG in their ability to prevent the adsorption of proteins. The covalent functionalization of poly(ethyleneimine) (PEI) that had been allowed to adsorb noncovalently to polystyrene with carbohydrates resulted in a decrease in the extent of protein adsorption to the polymer surface.<sup>33</sup> Several groups have also reported that surfaces presenting phosphorylcholine derivatives resist the adsorption of proteins.<sup>33-39</sup>

The next paragraph of Kane et al. (inserted below) goes on to propose "theories" that are "attempts" to explain protein resistance, but acknowledges that it would be desirable to explain or rationalize the protein resistance of others of the known protein-resistant surfaces. Nowhere are brush polymers suggested or disclosed.

**Mechanism of Protein Resistance.** Andrade and de Gennes developed a model to rationalize the protein resistance of surfaces grafted with PEG on the basis of ideas derived from the colloid stabilization literature.<sup>22</sup> The conformational flexibility of the grafted PEG is an important component of their model. Their model is applicable only to surfaces grafted with *long* polymer chains and does not explain the protein resistance of SAMs presenting short oligo(ethylene glycol) chains  $-(EG)_nOH$

or  $-(\text{EG})_n\text{OCH}_3$ ,  $n = 3-6$ ). Szleifer et al.<sup>18-20,40</sup> claimed that, by using single-chain mean field theory for the polymer chains, it was also possible to rationalize the protein resistance of surfaces (e.g. SAMs) presenting a high density of short  $(\text{EG})_n\text{OH}$  chains ( $n < 7$ ). Grunze et al.<sup>13-17</sup> proposed that the interaction of water with the surface of SAMs presenting oligo(ethylene glycol) groups is a more important determinant of protein resistance than the steric stabilization provided by the terminal oligo(ethylene glycol) chains. These theories<sup>16,18,19,21,22</sup> are attempts to explain the protein resistance of surfaces displaying PEG or oligo(ethylene glycol) groups; it would be desirable to explain or rationalize the protein resistance of others of the known protein-resistant surfaces and to provide leads to new protein-resistant surfaces.

Kane et al. go on to state a "Kosmotrope" theory of protein resistance, but nowhere suggest the use of brush polymers in the context of the presently claimed invention. Indeed, in their final two paragraphs on page 2391 (inserted below), Kane et al. acknowledge the limited data and confounding factors (e.g., attached to surface versus not attached) that may be problematic in their theory, or limit it to only the particular materials studied.

## Discussion

On the basis of a survey of ~50 organic functional groups, Chapman et al.<sup>2,3</sup> noted that several different types of organic functional groups can form the basis of surfaces that resist protein adsorption. The observation that most of the known protein-resistant surfaces are based on displays of kosmotropes is compatible with the results of this survey. The molecular basis for kosmotropicity is also probably not the same for every solute; several organic solutes (e.g. zwitterionic osmolytes such as betaine, and neutral polymers such as PEG) are kosmotropes.<sup>2,3,8,42,50</sup> For instance, the conformational flexibility of PEG may contribute to its preferential exclusion and kosmotropicity,<sup>42</sup> and to the protein resistance of surfaces functionalized with PEG;<sup>9,21,22</sup> conformational flexibility is, however, *not* a prerequisite for kosmotropicity of a solute, and is also not *required* for protein resistance of a surface,<sup>2,3</sup> although it may be important in certain cases. Our proposed link between kosmotropicity and the protein resistance of surfaces suggests that understanding the various mechanisms responsible for kosmotropicity will shed light on the mechanisms responsible for the resistance of surfaces to the adsorption of proteins.

## Conclusions

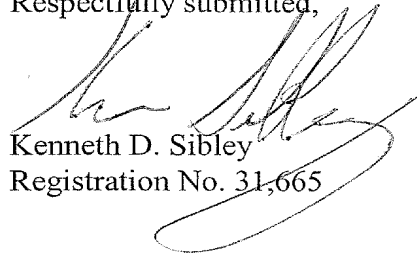
The hypothesis that molecules that are excluded from the protein-water interface (kosmotropes) themselves exclude proteins from surfaces to which they are attached is intuitively plausible. The data that are currently available with which to test this hypothesis are few, and there are substantial differences between molecules in solution and molecules attached (particularly at high density) to a surface. It is possible that the packing or orientation of the attached molecules may influence the protein resistance of the surface. Nonetheless, these data are sufficient to suggest a connection between these complex properties—protein resistance, kosmotropicity, and biological function as an osmolyte—that may illuminate all three.

Hawker et al. is said to disclose a method for covalent attachment for brush polymers as claimed, but not the anti-fouling brush polymer. Nevertheless, Hawker et al. does not make up the deficiencies of Kane et al. in the above-cited rejection. Indeed, Hawker et al. is concerned with the problem of SAM barrier layers that are less prone to defect formation, have better barrier properties when using dry etchants such as reactive ions, etc. (see column 1 lines 39-62). Nowhere is Hawker et al. concerned with protein resistance.

In view of the foregoing, it is respectfully submitted that this rejection should be withdrawn.

It is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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Attachments: Replacement Drawings (4 sheets)